CLINICAL & GENETIC PATTERNS OF GAUCHER DISEASE IN KURDISTAN REGION

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ABSTRACT

Background: Gaucher disease is a rare autosomal recessive lysosomal storage disease and the most frequent form of the sphingolipidoses owing to lysosomal glucocerebrosidase enzyme activity insufficiency that is attributed to glucosylceramidase beta (GBA1) gene imperfection. As yet, close to 460 pathological variations as mutations have been perceived. This study worked towards assessment of phenotypic characteristic and genetic constitution of patients with Gaucher disease in Kurdistan region.

Patients and methods: This cross-sectional study involved 23 patients; all were assessed for β- glucocerebrosidase enzyme level. Patients with reduced enzyme level were further evaluated to verify the diagnosis of Gaucher disease through molecular genetic analysis.

Results: Hepatosplenomegaly, anaemia, pallor, and thrombocytopenia were reported in (95.7%) of cases. The mutation c. 1448T>C in homozygous status was ascertained in (34.8%) of Gaucher cases. The genotype c.1246G>A in homozygous status was determined in (30.8%) of cases with Kurdish descent. The difference in the genetic composition of the three ethnic groups was significant (P=0.062).

Conclusion: The prime mutation in patients with Gaucher disease in Kurdistan Region was c. 1448T>C. The Gaucher disease type-1- was verified as prevailing phenotype of Gaucher disease.

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Keywords: Gaucher disease; Genetic mutation; Glucocerebrosidase enzyme.

Gaucher disease is a rare hereditary lysosomal storage disorder occurs principally due to defect in Glucosylceramidase beta[1] (GBA1) gene inducing defective activity of the acid β-glucosidase enzyme and secondarily due to mutations in the sphingolipid activator protein SAP C gene[1,2]. Conventionally the acid β-glucosidase enzyme degrades the glucosylceramide into glucose and ceramide. On the contrary, in Gaucher disease (GD) impaired function of acid β-glucosidase enzyme gives rise to building up of glucosylceramide in the lysosomes of macrophage cells having the effect that transfiguration to Gaucher cells which will rack up and damage multiple organ system all over the body chiefly the reticuloendothelial system (liver, spleen, bone marrow) and cerebral grey matter[3,4,5]. Make an observation of epidemiology of GD, its prevalence in general population is around 0.39 to 5.80 per 100 000 with high-rise in Ashkenazi Jewish ancestry with a birth incidence of approximately 1 in 350–450[6,7]. On the report of the age of onset, presence/absence, and progression of neurologic manifestations; GD is rated to three clinical types: non-neuropathic type-1- as the most common variety, acute neuronopathic type-2- and chronic neuronopathic type-3-[8,9]. GD exhibits clinical heterogeneity fluctuating from severe forms at birth to very mild phenotypes[10]. GD type-1- clinical properties demonstrate as abdominal distention on account of hepatosplenomegaly, anemia, bleeding

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tendencies (epistaxis, bruising), delayed growth, delayed puberty, pulmonary complications (pulmonary hypertension and hepatopulmonary syndrome), gaucheroma and bone involvement with acute painful bone crisis, osteopenia, osteoporosis, bone infarctions, pathological fractures, and avascular necrosis[4,11,12,13]. In the face of the fact that GD type -1- is non-neuropathic, it attracts the attention that there is central nervous system involvement in this type (e.g., Parkinson disease and Lewy body dementia)[10,14]. Type -2- GD does not have racial preference and is marked clinically either prenatally (fetal death) or perinatally (as hydrops fetalis and congenital ichthyosis) or in the first few months of life by severe rapidly progressive central nervous system involvement and systemic manifestations[15,16]. Expeditious neurological signs and symptoms of type-2- GD demonstrate as brain stem dysfunction which include supranuclear gaze palsy, irritability, hypertonia, hypokinesia, dysphagia, stridor, convergent strabismus, and seizures with myoclonus[17,18]. Moreover, patients with GD type-3- present with a greater extent serious critical somatic signs and symptoms of type-1- GD, but gradual neurological manifestations including cognitive impairment, myoclonic seizures, ataxia, spasticity, slow horizontal saccade, and muscle weakness develop[19]. The diagnosis of GD is set up on illustration of low acid β-glucosidase activity in blood leukocytes, cultured skin fibroblasts, or dried blood spotting (DBS) using synthetic substrates and tandem mass spectrometry[4,11]. Over and above that, diagnosis of GD is verified by molecular genetic testing by way of single gene testing or multigene panel[20]. On condition that glucosidase activity is normal but clinical characteristics point to GD with increased biomarkers activity, the very rare saposin C deficiency should be suspected, the diagnosis of which is made by prosaposin (PSAP) gene sequencing[21]. Present-day remedies include enzyme replacement therapy and substrate reduction therapy; both are not effectual in type 2 and 3 GD as they cannot infiltrate the blood-brain barrier[22,23]. Interestingly there is notable genetic mutation-geographical distribution relationship, the ultimate prevailing genetic species in Ashkenazi Jewish is c. 1226A> G while c.84dup insertion (q approximately 0.003) occurs exclusively in this population, inversely Asian communities evinced c. 1448T>C, c.754T>A, c. 1483G>C, and c. 1497G>C mutations as universal genetic transmutation[24,25]. There is remarkable genotype-phenotype correlation for e.g., c. 1226A> G and c. 608A>G mutations are related with Type 1 GD as well as c. 1448T>C mutation is linked with Type- 2-GD[25]. Our study is targeted to realize the principal genetic mutation among patients, the predominant subtype, most presenting clinical features and the genotype-phenotype correlation of GD in our region.

PATIENTS AND METHODS:

This cross-sectional study was accomplished in Kurdistan Rare Diseases Center at Raparine Teaching Hospital in Erbil city from March 2019 till April 2022. Data were gathered through particularly designed questionnaires during interviews with the patients and their families, the chief source of information was the parents. Important points in history were focused on age at presentation, age at diagnosis, symptoms at presentation, family history, and history of consanguinity. Anthropometric measures were measured and plotted on growth charts for all patients. All patients were evaluated through initial investigations relative to their complaints and

presentation including complete blood picture, liver function test, bleeding profile, and abdominal ultrasound. Determinative investigations including β-glucosidase enzyme activity were accomplished for all cases who possess strong clinical suspicion of GD. β-glucosidase enzyme activity was quantified by utilizing DBS cards via Tandem mass spectrometry method that was undertaken by a well-trained nurse by venous blood sampling. Consequently, the blood is spotted on the DBS card onto the sample collection area which is recessed area with four printed circles and should be dried for at least 4 hours at room temperature. The information on the DBS card were filled by the same nurse including patient name, sex, date of birth, patient identification number, requesting physician name, hospital name and country. Eventually the cards were shipped abroad to be tested (by a private company). β-glucosidase enzyme activity was stated as micromoles of product per liter of whole blood per hour (μmol/l/h). As the same time as the acid β-glucosidase enzyme activity was decreased (cut-off value of normal enzyme level is > 1.5μmol/L/h)[26], molecular genetic analysis was done to prove the diagnosis of GD through next-generation sequencing (NGS) by utilizing the same sample of DBS.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Fisher's exact test was used (instead of the Chi square) when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. A p value of ≤ 0.05 was considered statistically significant.

RESULTS:

The mean age (SD) was 13.5 (10.9) years. The median age was 13.4 years, and the age range was 1.3-43.0 years. Furthermore two-third of the cases were aged (<5 years) and (>20years). More than half of the cases (60.9%) were female. It is important to note that Erbil, Duhok and Sulaimaniya have approximately equivalent number of cases (34.8%, 30.4% and 30.4%) respectively. It is apparent that about half (56.5%) of the cases were Kurdish and only a third (34.8%) of cases were Arabic. Not more than 4 cases (17.4%) were presented as part of screening for GD. At most 9 cases (39.1%) were splenectomised. Over half of the parents (56.5%) were consanguineous and around third of the cases (30.4%) have more than 3 family members affected with GD. (Table 1)

Table 1: Basic characteristics of patients with Gaucher disease

Age (years)	No.	(%)
< 5	7	(30.4)
5-9	3	(13.0)
10-14	3	(13.0)
15-19	3	(13.0)
≥ 20	7	(30.4)
Gender		
Male	9	(39.1)
Female	14	(60.9)
Address		
Erbil	8	(34.8)
Duhok	7	(30.4)
Sulaimani	7	(30.4)
Halabja	1	(4.3)

Age (years)	No.	(%)
Ethnic group		
Kurdish	13	(56.5)
Arabic	8	(34.8)
Turkman	2	(8.7)
Presentation as part of screening		
Yes	4	(17.4)
No	19	(82.6)
History of splenectomy		
Yes	9	(39.1)
No	14	(60.9)
Parents consanguinity		
Consanguineous parents	13	(56.5)
Non-consanguineous parents	10	(43.5)
Family history of GD		
Negative family history	7	(30.4)
1 affected family member	5	(21.7)
>1 family member affected	4	(17.4)
>3 affected family member	7	(30.4)
Total	**23**	**(100.0)**

It is crystal clear in table (2) that the most common presenting symptoms were hepatosplenomegaly, anemia, pallor, and thrombocytopenia. Abdominal distension was recognized in 18 cases (78.3%). It is quite apparent in this table that chronic fatigue and growth retardation were nearly ascertained (69.6% and 65.2%) respectively. Along with it is stated that delayed puberty (21.7%) and epistaxis (17.4%) were in proximity among the patients of GD. Moreover, this table showed that the least common symptoms among patients with GD were bruising, gum bleeding and hepatopulmonary syndrome (8.7%, 4.3% and 4.3%) respectively.

Table 2: Clinical presentations of Gaucher disease.

	No.	(%) N = 23
Hepatosplenomegaly	22	(95.7)
Anemia	22	(95.7)
Pallor	22	(95.7)
Thrombocytopenia	22	(95.7)
Abdominal distension	18	(78.3)
Chronic fatigue	16	(69.6)
Growth retardation	15	(65.2)
Delayed puberty	5	(21.7)
Epistaxis	4	(17.4)
Bruising	2	(8.7)
Gum bleeding	1	(4.3)
Hepatopulmonary syndrome	1	(4.3)

It is evident in Table (3) that the largest proportion (34.8%) of the sample were of ‘c. 1448T>C homozygous type’ (62.5% of the Arabs, 23.1% of the Kurds, and none of the Turkman). Around one fifth (21.7%) were of ‘c. 1226A> G homozygous’ type (100% of the Turkman, 15.4% of the Kurds, and 12.5% of the Arabs). The differences were close to the level of significance (p = 0.062) in spite of these

differences, and this could be due to the small sample size. Mutation type was missense in all the cases except 15.4% of cases showing combined (missense & synonymous) (Table 3).

Table 3: Molecular genetic analysis and gen etic mutation by ethnicity

Genetic Mutation	Protein Change	Zygosity	Mutation Type	Ethnicity			Total	*p*-value *
				Kurdish	Arabic	Turkman		
Not available				0 (0.0)	2 (25.0)	0 (0.0)	2 (8.7)	
c. 1226A> G	p.(Asn409Ser)	Homozygous	Missense	2 (15.4)	1 (12.5)	2 (100.0)	5 (21.7)	
c. 1205A>G	p.(Tyr402Cys)	Homozygous	Missense	1 (7.7)	0 (0.0)	0 (0.0)	1 (4.3)	
c. 1448T>C	p.(Leu483Pro)	Homozygous	Missense	3 (23.1)	5 (62.5)	0 (0.0)	8 (34.8)	
c. 1246G>A	p.(Gly426Ser) (p.Leu483Pro, p.Ala495Pro,p. Val499=)	Heterozygous	Combined (Missense & Synonymous)	2 (15.4)	0 (0.0)	0 (0.0)	2 (8.7)	
c. 1246G>A	p.(Gly426Ser)	Homozygous	Missense	4 (30.8)	0 (0.0)	0 (0.0)	4 (17.4)	
c. 1228C>G	p.(Leu410Val)	Homozygous	Missense	1 (7.7)	0 (0.0)	0 (0.0)	1 (4.3)	0.062
Total				13 (100.0)	8 (100.0)	2 (100.0)	23 (100.0)	

*By Fisher's exact test.

DISCUSSION:

This present study delineated the most common clinical properties and genetic mutations in GD in Kurdistan region. Two age groups (<5 years) and (>20years) were dominantly concerned in this study that totally agreed by Thejeal et al 27 but contradicted by Alasmar 5 as it showed all patients' age below 8 years. In our region the principal race is Kurdish, on account of that, this inquiry perceived over half of the cases from Kurdish ancestry. It is important to highlight that prolonged duration between the commencement of the symptoms and diagnosis in several of the patients in this study generates developing complications of the disease, consequently those patients were splenectomised. The number of the splenectomised patients in our study were within close range to that of Thejeal et al 27 but far away from the results of Piran et al 28. In our culture, consanguine marriage is a tradition, accordingly our study declared consequential parental consanguinity-Gaucher disease prevalence association, unlike what Sheth et al 29 found (parental consanguinity was observed only in quarter of patients) but imminent of the discovery of Tunisian study (64.94%) 30. This contemporary study clued in the familial component of GD, entirely was dissimilar Alasmar 5 (only 2 patients had positive family history of GD). It is well recognized certainty that GD is known to be in possession of three clinical varieties (1, 2 and 3), despite that our recent study made out the non-neuropathic type -1- as the sole clinical pattern in our region in defiance of Turkish study 31 announced equivalent pervasiveness of both type 1 and 3 (GD1/GD3 = 20/18) but simultaneously near the outcome of Feng et al 25. This study showed beyond no doubt that hepatosplenomegaly, anemia, pallor, and thrombocytopenia were the most prevalent hallmarks among the presenting features of our patients, was on the same opinion of Thejeal et al 27 and an Egyptian study 32. It is worth mentioning that growth retardation is one of the obstacles that face patients with GD, late diagnosis along with delayed initiation and cut in treatment

were factors that escalate growth retardation in our patients, this went along with the findings of Alasmar 5. Delayed puberty is defined as absence of thelarche by age of 13 years and menarche by 15 years in girls and absent testicular development by age of 14 years in boys 33, so it was not noteworthy characteristic in our patients as around three quarter of them are less than 14-year. Nevertheless, the platelets count was low in nearly all patients in this analysis, barely they exhibited features of bleeding tendencies in disagreement with Feng et al 25 (>63% showed bleeding propensities). As a matter of interest, at most one patient experienced hepatopulmonary syndrome as complication of GD on the contrary of the Turkish study 31 (20% of cases have pulmonary involvement). Notwithstanding the fact that bone involvement is widely known manifestation and complication of GD with wide range of presentations, astonishingly our study showed no such manifestations in patients of GD which absolutely antagonized by Giraldo et al 34 (>53% of Gaucher disease type-1- have bone diseases and complications). This study recognized five different genetic mutations of the GBA1 gene with both homozygous and heterozygous status. The most common mutation was c. 1448T>C homozygous that entirely matched with the findings of Fateen et al 35 and Alai et al 36 but was in dispute with Hannah et al 37 that proclaimed 1226A> G as the most common genetic mutation in Ashkenazi Jewish. The second significant mutation was the homozygous c. 1226A> G followed by c. 1246G>A homozygous mutation. A consequential ethnic group-genetic mutation interrelation with statistical significance was stated in this study, as there is noticeable dissimilarity between the three ethnic groups (Kurdish, Arabic and Turkman). As stated above the concomitant genotype with GD type-1- is 1226A> G and c. 608A>G, nevertheless our study submitted proof that 1448T>C mutation is linked with GD type-1-, quietly diverged from the Turkish study 31 (1226A> mutation is most common in CD type-1-) but close by the conclusion of Feng et al 25.

CONCLUSION:

Our study publicized 1448T>C as the ascendant genetic mutation affecting GD patients in Kurdistan Region. Noteworthy differences were shown between Kurdish and Arabic racial groups in the distribution of the genetic mutation. Type-1- GD was the exclusive subtype among patients with GD in this study exhibiting no bone or central nervous system manifestations. The foremost genotype-phenotype interrelation was association of 1448T>C with GD type-1-.

Conflict of Interest: No conflict of interest

Abbreviations

abbreviation	word
GD	Gaucher disease
GBA 1	Glucosylceramidase beta 1
DBS	Dried blood spotting
μmol	Micromol
h	hour

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پوختە

شێوازی کلینیکی و بۆماوەی گۆشەر لە هەرێمی کوردستان

پێشەکی و ئارمانج: نەخۆشی گۆشەر نەخۆشییەکی دەگمەنی عەمباری لایسۆسۆمیە لە باوانەوە و زۆرترین فۆرمی سفینگۆلیپیدۆسسە بە هۆی کەمبوونەوەی چالاکی ئەنزیمی گلوکۆسیربرۆسایدەیزی لایسۆسۆمی کە دەگەڕێتەوە بۆ ناتەواوی جینی گلوکۆسیلسیرامیدەیز بێتا (GBA1).تا ئێستا نزیکەی ٤٦٠ شێوە گۆڕانی نەخۆشی وەک بازدانەکان هەست پێکراوە.ئەم توێژینەوەیە کاری کرد بەرەو هەڵسەنگاندنی تایبەتمەندی فینۆتایپ و دەستوری بۆماوەی نەخۆشەکانی نەخۆشی گۆشەر لە هەرێمی کوردستان.

نەخۆشەکان و شێوازەکان: ئەم توێژینەوە بڕبڕەییە ٢٣ نەخۆشی لەخۆ گرتووە هەموویان هەڵسەنگاندنیان بۆکرا بۆ ڕێژەی ئەنزیمی بێتاگلوکۆسیربرۆسایدەیز ئەو نەخۆشانەی ئاستی ئەنزیمەکەیان کەمتر بوو لە ڕێژەی ئاسای بۆ پشتڕاستکردنەوەی دەست نیشانکردنی نەخۆشیەکە هەڵسەنگاندنی زیاتریان بۆ کرا لە ڕێگەی شیکاری گەردیلەی بۆماوەی.

ئەنجامەکان: گەورەبوونی سپڵ و جگەر ، کەمخوێنی ، سپی هەڵگەڕان و کەمبوونەوەی پەڕەکانی خوێن لە ٩٥,٧٪ حاڵەتەکان تۆمار کراون .بازدانی c. 1448T>C لە دۆخی هاوزاگۆسیدا لە ٣٤,٨٪ حاڵەتەکانی گۆشەردا دڵنیاکرایەوە. جینۆتایپی c.1246G>A لەدۆخی هاوزایگۆسیدا لە ٣٠,٨٪ ی حاڵەتەکانی بەڕەچەڵەک کورد دیاریکرا. جیاوازی لە پێکهاتەی بۆماوەی سێ گرووپی نەتەوەیەکەدا بەرچاوو بوو P=0.062.

دەرێەنجام: بازدانی سەرەکی لە نەخۆشانی گۆشەر لە هەرێمی کوردستان c.1448>C. نەخۆشی گۆشەری جۆری ١ وەک فینۆتایپی گشتگیری نەخۆشی گۆشەر پشتڕاستکرایەوە.

الخلاصة

الأنماط السريرية والوراثية لمرض غوشيه في إقليم كردستان

الخلفية والأهداف: مرض غوشيه هو مرض تخزين الليزوزومية المتنحية النادرة وهو الشكل الأكثر شيوعًا من الشحميات السفينجولية بسبب قصور نشاط إنزيم الجلوكوسيربيروسيداز الليزوزومي الذي يعزى إلى خلل في جين الجلوكوزيل سيراميداز بيتا وحتى الآن، تم رصد ما يقرب من 460 اختلافًا في طفرة المرض. عملت هذه الدراسة على تقييم الخصائص المظهرية والتكوين الجيني للمرضى الذين يعانون من مرض غوشيه في إقليم كردستان.

المرضى والطرق: شملت هذه الدراسة المقطعية 23 مريضا تم تقييم جميعهم لمستوى إنزيم الجلوكوسيربيروسيداز بيتا. تم تقييم المرضى الذين يعانون من انخفاض مستوى الإنزيم للتحقق من تشخيص مرض غوشيه من خلال التحليل الجيني الجزيئي.

النتائج: تم الإبلاغ عن تضخم الكبد الطحال، فقر الدم، الشحوب، ونقص الصفيحات في (95.7٪) من الحالات. تم التحقق من الطفرة c.1448T>C في حالة متماثلة الزيجوت في (34.8%) من حالات غوشيه. تم تحديد النمط الجيني c.1246G>A في حالة متماثلة الزيجوت في (30.8%) من الحالات ذات الأصول الكردية. كان الاختلاف في التركيب الوراثي للمجموعات العرقية الثلاث مهما (P = 0.062).

الخاتمة: كانت الطفرة الأولية في المرضى الذين يعانون من مرض غوشيه في إقليم كردستان هي c.1448T>C. تم التحقق من أن نوع مرض غوشيه -1- هو النمط الظاهري السائد لمرض غوشيه.